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Health and Environmental Effects Profile for Benzoyl Chloride

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR BENZOYL CHLORIDE

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16. ABSTRACT

The Health and Environmental Effects Profile for Benzoyl Chloride was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for benzoyl chloride.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. Existing data are insufficient to determine an RQ value.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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EXECUTIVE SUMMARY

Benzoyl chloride is a colorless liquid with a pungent odor, and is a lacrimator. It reacts spontaneously with water and ethanol to give benzoic acid, but is soluble in more inert solvents like ether, benzene and carbon disulfide (Hawley, 1981; Windholz, 1983). Currently, three U.S. companies are major producers of benzoyl chloride, although their U.S. production volume is unknown. In 1983, ~1.6 million pounds of benzoyl chloride was imported into the United States. Benzoyl chloride is produced photochemically by the reaction between toluene and chlorine and then by treating the resultant benzotrichloride with benzoic acid in the presence of zinc chloride. The compound is used primarily to synthesize benzoyl peroxide, and benzophenone and its derivatives, for use in the production of dyes, pharmaceuticals, resins, perfumes and polymerization catalysts (Williams, 1978).

Rapid hydrolysis will be the major fate of benzoyl chloride in aquatic media (Mabey and Mill, 1978). Hydrolysis is also expected to be its major terrestrial fate determining process. The hydrolysis products are benzoic and hydrochloric acids (Morrison and Boyd, 1973). In the absence of water, benzoyl chloride can react with soil constituents to form a variety of compounds. In the atmosphere, benzoyl chloride may photodegrade and react with hydroxyl radicals, and is also likely to undergo hydrolysis. Therefore, benzoyl chloride is not expected to persist in either air, water, soil or food.

Since benzoyl chloride is used as a reactive chemical intermediate and is not known to occur in any commercial product, no significant consumer exposure to benzoyl chloride is expected. An estimated 1008 individuals, however, are occupationally exposed to benzoyl chloride (RTECS, 1984).

The rapid hydrolysis and degradation of benzoyl chloride in water makes it difficult to assess its toxicity per se to aquatic organisms. Any toxic effects would probably be due to its breakdown products, benzoic and hydrochloric acids, rather than to benzoyl chloride itself (Curtis et al., 1979).

Rat studies have shown that benzoyl chloride or its hydrolysis product benzoic acid is rapidly absorbed from the gastrointestinal tract, metabolized and excreted primarily in the urine (Yu and Zinicki, 1979). After a single oral dose (^{14}C-benzoyl chloride, uniformly ring-labeled), peak levels of radioactivity in the body were attained within 1 hour. Elimination from the blood was first-order, with a $t_{1/2}$ of 1.5 hours. Very little radioactivity (~0.8% of the administered dose) was found in the tissues. Urinary elimination of radioactivity was first-order, with a $t_{1/2}$ of 7.5 hours. Principal metabolites included benzoic acid (70%) and hippuric acid (20%). After repeated dosing at 24-hour intervals, maximum concentrations were attained in the tissues (primarily kidney, liver, muscle and fat) within 1-4 days.

Pertinent data regarding the carcinogenicity of ingested benzoyl chloride could not be located in the available literature as cited in the Appendix. There is insufficient evidence to conclude that benzoyl chloride is carcinogenic (by inhalation or dermal routes of exposure) in mice (Fukuda et al., 1981; Yoshimura et al., 1979; Takemoto et al., 1978) or humans (Sakabe et al., 1976; Sakabe and Fukuda, 1977; Sorahan et al., 1983; Rockette and Arena, 1983; Wong and Morgan, 1984). There is, however, limited evidence that occupational exposure to benzoyl chloride may be associated with an increased risk of respiratory cancer in humans (Sakabe et al., 1976).

Since workers employed in benzoyl chloride or benzoyl peroxide production were also exposed to benzotrichloride which has been shown to cause cancer in mice by the pulmonary and dermal routes of exposure (Yoshimura et al., 1979; Takemoto et al., 1978; Fukuda et al., 1981), it is thought that benzotrichloride is the etiologic agent in these human respiratory cancers. Benzoyl chloride was not found to be mutagenic in bacterial assay systems (McMahon et al., 1979; Yasuo et al., 1978; Chiu et al., 1978; Kawazoe and Kato, 1982).

Pertinent data regarding the teratogenicity, reproductive toxicity and chronic or subchronic toxicity of ingested benzoyl chloride could not be located in the available literature as cited in the Appendix. Subchronic inhalation exposure of mice to 1.6 or 6.8 ppm (9.2 or 39.1 mg/m^3), 30 minutes/day, 2 days/week for 5 months may have resulted in hyperplasia of the tracheal epithilium or adenoids (Takemoto et al., 1978; Yoshimura et al., 1979), but the lack of control data compromises the reliability of these observations. In skin-painting studies designed to test the oncogenicity of benzoyl chloride, Fukuda et al. (1981) observed decreased motor activity in treated rats and mice; however, the reduction in motor activity may have been due to pain associated with movement (benzoyl chloride caused skin irritation including erythema, swelling, keratinization, alopecia, ulcers and epidermal necrosis), rather than to neurological effects per se. Benzoyl chloride is considered to be strongly irritating to the skin, eyes, nose and mucous membranes (ITII, 1975; Weiss, 1980).

On the basis of the cancer studies in animals and humans, benzoyl chloride is best classified as a Group D compound. The collective data were insufficient for use in the derivation of any other quantitative criteria (RQs, ADIs, potency factors).

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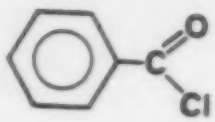
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
C_{max}	Body burden
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Median lethal concentration
LD_{50}	Median lethal dose
MATC	Maximum acceptable toxicant concentration
MED	Minimum effective dose
ppm	Parts per million
RMLT	Regression models in life tables
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SMR	Standard mortality ratio
TLV	Threshold limit value
$t_{1/2}$	Half-life

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Benzoyl chloride is also known as benzenecarbonyl chloride; benzoic acid, chloride; and alpha-chlorobenzaldehyde. The structure of benzoyl chloride is depicted below:



Molecular weight: 140.57

Empirical formula: C_7H_5ClO

The CAS Registry number for benzoyl chloride is 98-88-4.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Benzoyl chloride is a transparent, colorless liquid with a pungent odor (Hawley, 1981). Benzoyl chloride is a lacrimator (Windholz, 1983). Selected physical properties are listed below:

Melting point:	-1°C (Verschueren, 1983)
Boiling point:	197°C (Verschueren, 1983)
Specific gravity:	
at 15/15°C	1.22 (Verschueren, 1983)
at 25/4°C	1.2070 (Windholz, 1983)
Refractive Index, 20°C:	1.5536 (Hawley, 1981) 1.55369 (Windholz, 1983)
Vapor Pressure, mm Hg:	
at 20°C	0.4 (Verschueren, 1983)
at 32.1°C	1 (Weast, 1973)
at 59.1°C	5 (Perry and Green, 1984)
Water solubility:	Decomposes in water (Hawley, 1981; Windholz, 1983)
Non-aqueous solubility:	Decomposes in alcohol, miscible with ether, benzene, carbon disulfide and oils (Windholz, 1983)

Flash point (closed cup): 72.2°C (Sax, 1984)

Conversion factors (air): 1 ppm = 5.75 mg/m³
1 mg/m³ = 0.17 ppm

Benzoyl chloride will undergo a variety of nucleophilic substitution reactions yielding amides, esters and ketones (Morrison and Boyd, 1973).

1.3. PRODUCTION DATA

American companies that imported or produced benzoyl chloride in 1977 are listed in Table 1-1 (U.S. EPA, 1977) together with their locations and available information concerning production and import volumes. The total volume of benzoyl chloride imported into the United States in 1983 was 1.6 million pounds (USITC, 1984). As of January 1985, benzoyl chloride was produced by Kalama Chemical, Inc. in Garfield, NJ; Northwest Industries, Inc. (Velsicol Chemical Corp.) in Chattanooga, TN; Occidental Petroleum Corp. (Hooker Indust. & Specialty Chem.) in Niagara Falls, NY (SRI, 1985). Chemical Dynamics Corp. of South Plainfield, NJ is listed as a producer in Chemcyclopedia (1986).

Benzoyl chloride is commercially produced by the photochemical reaction between toluene and chlorine. The resulting benzotrichloride is then treated with benzoic acid in the presence of zinc chloride to produce benzoyl chloride. Benzoyl chloride can also be synthesized by the partial hydrolysis of benzotrichloride, the chlorination of benzaldehyde, and the reaction of benzoic acid with phosphorus pentachloride, phosgene or benzotrichloride (Williams, 1978).

1.4. USE DATA

Benzoyl chloride is used as a benzoylating agent to introduce the benzoyl radical into alcohols, phenols, amines and other compounds by the Friedel-Crafts and Schotten-Baumann reactions (Williams, 1978). It is also

TABLE 1-1

Production/Importation Data from the 1977 U.S. EPA TSCA Production File*

Manufacturer	Location	Production Volume millions of pounds (importer)
Velsicol Chemical Corp.	Chattanooga, TN	NR; NS
The Sieflor Corp.	Los Angeles, CA	0.1-1.0 (I)
Sakai Trading New York, Inc.	New York, NY	0 (I)
Hooker Chemical & Plastics	Niagara Falls, NY	10-50 (NS)
Drake Chemicals, Inc.	Lock Haven, PA	NR; NS
NI	NS	0.1-1.0 (NS)

*Source: U.S. EPA, 1977

I = Importer; NS = not specified whether it is imported or not; NR = not reported; NI = not identified

used in the production of benzoyl peroxide, benzophenone and derivatives for use in the production of dyes, resins, perfumes, pharmaceuticals and polymerization catalysts. Cellulosic yarns have been treated with benzoyl chloride for an unspecified purpose, and dyed fibers and fabrics display improved washfastness following treatment with benzoyl chloride (Williams, 1978). Benzoyl chloride is used as a reagent in organic analyses (Windholz, 1983) and in the synthesis of stabilizers (Chemcyclopedia, 1985).

1.5. SUMMARY

Benzoyl chloride is a transparent, colorless liquid with a pungent odor; it is a lacrimator. It decomposes in water and ethanol, but is soluble in ether, benzene, and carbon disulfide (Hawley, 1981; Windholz, 1983). Currently, three United States companies are major producers of benzoyl chloride, although their United States production volume is not known. In 1983, ~1.6 million pounds of benzoyl chloride was imported into the United States. Benzoyl chloride is produced by photochemically reacting toluene and chlorine and by reacting the resultant benzotrichloride with benzoic acid in the presence of zinc chloride. The compound is used primarily to synthesize benzoyl peroxide, benzophenone and its derivatives, used in the production of dyes, pharmaceuticals, resins, perfumes and polymerization catalysts (Williams, 1978).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

According to Mabey and Mill (1978), the hydrolysis rate constant and $t_{1/2}$ of benzoyl chloride at 25°C are 4.2×10^{-2} $seconds^{-1}$ and 16 seconds, respectively. The hydrolysis products are benzoic acid and hydrochloric acid (Morrison and Boyd, 1973). Hydrolysis is most likely the most significant aquatic fate process of benzoyl chloride because of the rapidity of this reaction. Since benzoyl chloride decomposes rapidly upon contact with water, it is not possible to obtain values for the water solubility, log K_{ow}, log K_{oc}, Henry's law constant on BCF for the compound. It is also not possible, therefore, to estimate the significance of photolysis, oxidation, volatilization, bioconcentration and biodegradation in determining the aquatic fate of benzoyl chloride. However, the $t_{1/2}$ of benzoyl chloride is very short because of hydrolysis; therefore, it is not likely that these other processes play a significant role in determining the fate of benzoyl chloride in the aquatic media.

2.2. AIR

Benzoyl chloride displays an absorption maximum at 282.9 nm (ϵ=1752) and a significant absorption at 293.0 nm (ϵ=1108) in methyl cyclohexane (Shashidhar, 1971). Benzoyl chloride also absorbs light in the vapor phase from 225-292 nm (Shashidhar, 1971). Benzoyl chloride may, therefore, photolyze in the atmosphere. Quantitative estimation of the $t_{1/2}$ due to this reaction cannot be calculated for the lack of available data. Because of its rapid hydrolysis in water, however, it is not likely to partition to the atmosphere from aquatic media. An atmospheric $t_{1/2}$ of 2.01 days was estimated because of the reaction of benzoyl chloride with hydroxyl radicals

(U.S. EPA, 1985). Because of its interaction with water in the atmosphere, benzoyl chloride is also likely to undergo hydrolysis; therefore, it will be short-lived in the atmosphere.

2.3. SOIL

The "Fragment Constant Method" of Leo and Hansch could be used to estimate an octanol water partition coefficient (K_{ow}) for benzoyl chloride; however, the resulting K_{ow} to K_{oc} correlation would be of little practical significance because of the short hydrolytic half-life of benzoyl chloride. As soil generally contains some water, hydrolysis is probably the predominant terrestrial fate of benzoyl chloride. As in the case of aquatic fate, it is unlikely that any common fate processes such as photolysis, oxidation or biodegradation will be more important than hydrolysis reaction. In the absence of water, benzoyl chloride may react with the humic materials in the soil to form a variety of compounds. Benzoyl chloride per se is not expected to persist in the soil.

2.4. SUMMARY

Rapid hydrolysis will be the major fate of benzoyl chloride in the aquatic media (Mabey and Mill, 1978). Hydrolysis is also expected to be its major terrestrial fate determining process. The hydrolysis products are benzoic acid and hydrochloric acid (Morrison and Boyd, 1973). In the absence of water, benzoyl chloride can react with soil constituents to form a variety of compounds. In the atmosphere, benzoyl chloride may photodegrade and react with hydroxyl radicals. It is also likely to undergo hydrolysis in the atmosphere. Therefore, benzoyl chloride is not expected to persist in either air, water or soil media.

3. EXPOSURE

Since benzoyl chloride is not known to occur in any commercial product, no significant consumer exposure to benzoyl chloride is expected. Exposure of the general population to benzoyl chloride from air, water and foods is not expected because benzoyl chloride is nonpersistent in air, water and soil. An estimated 1008 individuals, however, are occupationally exposed to benzoyl chloride (RTECS. 1984).

4. PHARMACOKINETICS

4.1. ABSORPTION

Yu and Zinicki (1979) gave uniformly ring-labeled ^{14}C-benzoyl chloride (single oral dose of 3.29 mg in 0.4 mℓ of olive oil) to Holtzman rats. Radioactivity peaked in the blood (4.1 ppm) within 1 hour of dosing and 56-90% of the administered radioactivity was excreted in the urine within 24 hours, indicating that benzoyl chloride was rapidly and extensively absorbed from the gastrointestinal tract.

4.2. DISTRIBUTION

Yu and Zinicki (1979) gave uniformly ring-labeled ^{14}C-benzoyl chloride (single oral dose of 3.29 mg in 0.4 mℓ of olive oil) to Holtzman rats. Radioactivity peaked in the blood (4.1 ppm) within 1 hour of dosing and fell to 0.02 ppm within 24 hours. Elimination from the blood was first-order with a $t_{1/2}$ of 1.5 hours. Within 8 hours of administration, ~0.8% of the administered radioactivity was found in kidney, liver, muscle, fat, brain, heart, spleen, ovary, uterus, lungs and skin. The $t_{0.95}$ for elimination from these tissues averaged 30 hours.

Body burden (C_{max}) was determined in rats after repeated dosing with ^{14}C-benzoyl chloride at 24-hour intervals (Yu and Zinicki, 1979). Maximum concentrations (indicated by ^{14}C-radioactivity) in the tissues were achieved after 1-4 days of dosing, with an average of 2 days. C_{max} for kidney, liver, muscle, fat and other tissues was 9.9, 0.34, 0.16, 0.38 and ~0.7 ppm, respectively.

4.3. METABOLISM

Yu and Zinicki (1979) gave uniformly ring-labeled ^{14}C-benzoyl chloride (single oral dose of 3.29 mg in 0.4 mℓ olive oil) to Holtzman rats. Most of the radioactivity was recovered in the urine within 24 hours of administration. Ninety-six percent of the urinary ^{14}C was recovered as freely

extractable metabolites: 70% benzoic acid, 21% hippuric acid and 5% unidentified. The hippuric acid was derived from benzoic acid, either through normal metabolism in vivo or from hydrolysis during the collection of urine. Water soluble metabolites (1.4%; unspecified) and acid-released metabolites (1.5%; unspecified) were also recovered from the urine.

4.4. EXCRETION

Yu and Zinicki (1979) gave uniformly ring-labeled ^{14}C-benzoyl chloride (single oral dose of 3.29 mg in 0.4 mL of olive oil) to Holtzman rats. Most of the administered ^{14}C was eliminated in the urine (56-90%) within 24 hours and in the feces (0.4-2%) within 48 hours after administration. Elimination was first-order, with a $t_{1/2}$ of 7.5 hours.

4.5. SUMMARY

Yu and Zinicki (1979) studied the pharmacokinetics of benzoyl chloride in rats. They showed that benzoyl chloride or its hydrolysis product, benzoic acid, is rapidly and extensively absorbed from the gastrointestinal tract, metabolized and excreted. Within 24 hours, 56-90% of the administered dose was excreted in the urine. The primary metabolites were benzoic acid (70%) and hippuric acid (21%). The compound was found to be widely distributed throughout the tissues of the rat. Elimination from the urine was first-order with a $t_{1/2}$ of 7.5 hours.

5. EFFECTS

5.1. CARCINOGENICITY

The Japanese literature contains reports which suggest that employment in the production of benzoyl chloride is associated with an increased risk of lung cancer. Sakabe et al. (1976) reported two cases of lung cancer in 41 workers employed in the production of benzoyl chloride from 1954-1972 (Table 5-1). These workers were in their forties and had been employed for 6-15 years. The time between last exposure and diagnosis of cancer ranged from 6-18 years. The two individuals with lung cancer were smokers and had been exposed to other chemicals including benzotrichloride, toluene, hydrochloric acid, benzal chloride and benzyl chloride. Using national (Japanese) rates for lung cancer, Sakabe et al. (1976) reported an expected value of 0.06 cases (Relative risk = 33.3, p=0.002). If all workers in the plant (n=147) were included in the cohort, the expected value is 0.22 (Relative risk = 9.1, p=0.02). In addition to the two cases of lung cancer, one case of squamous cell carcinoma of the bronchus and one case of maxillary malignant lymphoma were also found in the benzoyl chloride production workers; both of these individuals were nonsmokers. Sakabe et al. (1976) considered these four cases of cancer to be related to the benzoyl chloride production process. However, there was no direct evidence available that these four cases of cancer were due solely to benzoyl chloride exposure, nor was any evidence of a dose-response relationship provided by the authors. Analyses were conducted solely on the basis of expected number of lung cancer deaths for all workers vs. the number observed in benzoyl chloride production workers.

Sakabe and Fukuda (1977) reported two cases of lung cancer in another plant where benzoyl chloride and benzoyl peroxide were produced. Both

TABLE 5-1

Lung Cancer in Workers Employed in Benzoyl Chloride Production[a]

Exposure Route	Size of Exposed Population	Size of Control Population	Sex	Level of Exposure	Duration of Exposure (years)	Tumor Type	Number of Tumors Observed	Number of Tumors Expected	Relative Risk (p value)[b]
Occupational	41 (benzoyl chloride workers only)	NR (Japanese nationals)	M	NR	6-15	histologically undefined	2	0.06	33.3 (0.002)
Occupational	147 (all workers)	NR (Japanese nationals)	M/F	NR	6-15	histologically undefined	2	0.22	9.1 (0.02)

QUALITY OF EVIDENCE

Strengths of Study: Study attempts to relate observed values with expected values derived from the general population (Japanese nationals)

Weaknesses of Study: Both individuals with cancer were smokers and were exposed to other chemicals, including benzotrichloride, a suspected carcinogen. No induction-latent period was allowed for; therefore, the number of tumors expected may be overestimated. A third case of lung cancer was not included in the analysis.

Overall Adequacy: limited

Comments: The association between lung cancer and benzoyl chloride production is supported by two cases of lung cancer in men employed in benzoyl chloride production in another plant (Sakabe and Fukuda, 1977).

[a]Source: Sakabe et al., 1976

[b]The p values were obtained from IARC, 1982

individuals were male; one was a smoker, the other was not. The nonsmoker was employed in the manufacture of benzoyl peroxide for 4 years, followed by production of benzoyl chloride for 1 year. His cancer was diagnosed 11 years after exposure (35 years of age). The smoker was employed in the manufacture of benzoyl peroxide for 17 years and intermittently in the manufacture of benzoyl chloride for 7 years. His cancer was diagnosed 6 years after exposure was terminated (40 years of age). The number of workers in the plant varied from 13 in 1952 to 40 in 1963. As in the previous cases reported by Sakabe et al. (1976), the workers were also exposed to other chemicals including benzotrichloride.

Recently, Sorahan et al. (1983) reported the results of a mortality study relating exposure to mixed chlorinated toluenes in an organic chemical factory. Male workers were exposed to benzoyl chloride, benzal chloride, benzyl chloride and benzotrichloride. The study evaluated a total of 953 employees, which included 163 exposed and 793 nonexposed employees from 1923-1970. The mortality rates were compared with an external standard (SMR calculated from mortality rates for England and Wales) and an internal standard using RMLT method (Table 5-2). Using the SMR approach, Sorahan et al. (1983) found that the exposed workers and the nonexposed workers had significantly elevated SMRs for all causes (25 observed vs. 15.4 expected) and all cancers (10 observed vs. 3.93 expected) as compared with general mortality in England and Wales. Using the RMLT method an increased risk of mortality from cancer was observed only in exposed workers employed before 1951. The incidence of cancer was primarily of the respiratory and digestive system. The causative agent was believed to be benzotrichloride.

TABLE 5-2

Digestive and Respiratory Cancers in Occupationally Exposed Humans*

Size of Exposed Population	Size of Control Population	Sex	Level of Exposure	Duration of Exposure	Target Organ	Tumor Type	Number of Cases Observed	Number of Cases Expected	Relative Risk (p value)
163	England and Wales mortality rates	M	1-10 ppm	6 months to >40 years	digestive system	cancer	5	1.24	SMR=403 ($p<0.05$)
					respiratory system	cancer	5	1.78	SMR=281 ($p<0.05$)
					digestive and respiratory system	cancer	10	3.98	SMR=251 ($p<0.01$)

QUALITY OF EVIDENCE

Strengths of Study: Time- and age-specific comparison between the exposed group and national mortality rates was conducted. The increase in tumors of the digestive and respiratory systems are corroborative with the tumorigenesis seen in mice.

Weaknesses of Study: Exposure was to several chlorinated toluene compounds but benzotrichloride was the etiologic agent. The number of deaths is small.

Overall Adequacy: Limited

*Source: Sorahan et al., 1983

Similar results were reported by Rockette and Arena (1983) in males occupationally exposed to benzoyl chloride, benzal chloride, benzotrichloride and chlorinated toluene as well as other chemicals. Size, smoking history and other pertinent characteristics (age, dates of employment, etc.) of the cohort were not reported. Significantly elevated SMRs for respiratory cancer were observed in workers exposed for 75 years (Table 5-3) while significantly elevated SMRs were reported for larynx cancer in employees exposed for <5 years. In a group exposed ≥20 years, significantly elevated SMRs were also obtained. It should be noted that elevated incidence of respiratory cancer was observed for the entire plant, and no chemical was considered responsible.

Wong and Morgan (1984) evaluated the mortality rates of 697 male workers employed from 1943-1982 at Velsicol Chemical Corporation's chlorination plant in Chattanooga, Tennessee (Table 5-4). Mortality rates for the U.S. male population were used for comparison. The SMR for the cohort for all cancers combined was not statistically significant; however, the SMR for respiratory cancer was marginally significant. When the cohort was analyzed according to specific occupations, it was found that mortality from respiratory cancer was higher among maintenance workers than those in operation or production positions and that mortality from lung cancer was highest among laboratory employees. An analysis by chemical suggested that employees exposed to benzotrichloride, benzyl chloride and benzoyl chloride experienced an increased risk of respiratory cancer; however, since employees were exposed to all three chemicals, a specific agent could not be identified. The contribution of smoking to respiratory cancer could not be evaluated.

TABLE 5-3

Respiratory, Lung and Laryngeal Cancers in Occupationally Exposed Humans[a]

Size of Exposed Population	Size of Control Population	Sex	Level of Exposure	Duration of Exposure	Target Organ	Number of Tumors Observed	Number of Tumors Expected	Relative Risk[b]
NR	NR	M	NR	>5 years	respiratory system	11	4.89	SMR=225.1
					lung	10	4.61	SMR=216.9
				<5 years	larynx	3	0.58	SMR=518.8
				>5 plus <5 years with ≥20 years latency	respiratory	17	8.03	SMR=211.7
					lung	14	7.60	SMR=184.2
					larynx	3	0.36	SMR=826.1

QUALITY OF EVIDENCE

Strengths of Study: Analyzed data by duration of exposure and considered latency.

Weaknesses of Study: Cohort size not reported, control group not specified, exposure levels not quantified, employees were exposed to benzal chloride, benzotrichloride, benzyl chloride, chlorinated toluene residuals and others. High rates of respiratory cancer also occurred in other departments where employees were not exposed to these particular chemicals. Smoking history was not reported.

Overall Adequacy: Inadequate

[a]Source: Rockette and Arena, 1983

[b]p values were not reported but the SMRs were significant.

TABLE 5-4

Respiratory Cancers in Males Employed at Velsicol Chemical Plant for ≤40 Years[a,b]

Size of Exposed Population	Duration of Exposure (person years)	Number of Tumors Observed	Number of Tumors Expected	SMR (p value)
697 (total cohort)	9770.5	7	2.84	246.3 (borderline significance)
408 in operations/ production jobs	5892.2	2	1.12	178.2 (NS)
502 in maintenance jobs	7025.4	5	2.19	228.7 (NS)
58 in laboratory jobs	NR	2	0.15	1292.5 ($p \leq 0.05$)
669 ever in jobs with potential exposure to benzotrichloride	9287.1	7	2.69	260.1 ($p \leq 0.05$)
662 ever in jobs with potential exposure to benzyl chloride	9277.3	7	2.69	259.9 ($p \leq 0.05$)
670 ever in jobs with potential exposure to benzoyl chloride	9293.9	7	2.69	259.6 ($p \leq 0.05$)

QUALITY OF EVIDENCE

Strengths of Study: Cohort divided into appropriate groupings, an attempt to identify a specific agent was made.

Weaknesses of Study: Small cohort size, exposure levels not quantified, smoking history not evaluated, majority of cohort potentially exposed to all three suspect chemicals.

Overall Adequacy: Inadequate

[a]Source: Wong and Morgan, 1984

[b]The U.S. male mortality rates were used for comparisons.

Two inhalation studies and two skin-painting studies were conducted on mice to assess the carcinogenic potential of benzoyl chloride. The inhalation studies were translated from Japanese and reported by Hooker Chems and Plastic Corp. (1980). As part of a study on benzotrichloride, Takemoto et al. (1978) exposed a group of 20 female ICR mice (5 weeks of age) by inhalation to 6.8 ppm (39.1 mg/m³) benzoyl chloride 2 times/week, 30 minutes/exposure for 5 months. Mice were kept for up to 10 months and then sacrificed and examined histologically. The only results reported were that "all 20 animals were free of lung cancer" and that mild adenoid proliferation was observed in 2/10 mice at the end of 10 months. The majority of the study focused on the effects of benzotrichloride; further details regarding benzoyl chloride were not reported.

In another inhalation study designed to investigate the carcinogenic potential of benzotrichloride, Toshimura et al. (1979) exposed 28 female ICR-JCL mice to benzoyl chloride 2 times/week, 30 minutes/exposure for 5 months, followed by observation for ~1-9 additional months. Although the exposure concentration of benzoyl chloride was not specified, it was implied that the concentration was the same as that of benzotrichloride, which was 1.6 ppm. No lung tumors were observed in 8 mice that died or were sacrificed after 6 months or in 13 mice that died or were sacrificed after 10 months. One pulmonary adenoma and two malignant lung tumors were observed in 7 mice that survived until 14 months. No control mice were included in the study; further details of the study were not reported.

Fukuda et al. (1981) conducted two skin-painting experiments with benzoyl chloride on female specific pathogen-free ICR mice. In the first of these experiments, groups of 10 mice (3 weeks of age) were treated topically with either 10 µl of benzoyl chloride or 10 µl of 50% benzoyl chloride

in benzene (5 µl of benzoyl chloride) or benzene alone. Solutions were applied to the shaved backs of the mice 3 times/week for 4 weeks, then 2 times/week until they were sacrificed at the end of 9.8 months. Lungs and any grossly determined tumors were examined histologically. The incidence of lung tumors was 0/10, 0/10 and 3/10 for benzene controls and mice exposed to 5 and 10 µl of benzoyl chloride, respectively. The lung tumors were adenomas. The incidence of skin tumors was 0/10, 2/10 and 0/10 in the control, low- and high-dose group, respectively. The skin tumors were classified as one papilloma and one squamous cell adenoma.

In the second skin-painting experiment by Fukuda et al. (1981), groups of 20 female (specific pathogen-free) ICR mice (7 weeks of age) were treated with either 2.3 µl benzoyl chloride in 25 µl benzene or 25 µl benzene alone. Solutions were applied 2 times/week for 11.7 months. Mice were sacrificed after a subsequent 7 months of observation and examined for tumors. Lungs and any grossly identified tumors were examined histologically. Tumors were observed in 2/20 controls (lung adenomas) and in 7/20 exposed animals (two with squamous cell carcinoma; five with lung adenoma). On the basis of these studies, Fukuda et al. (1981) concluded that benzoyl chloride is a weak carcinogen.

On the basis of the human data and mouse skin-painting studies, IARC (1982a) has concluded that there is insufficient evidence to support the carcinogenicity of benzoyl chloride in animals or humans. The inhalation studies in mice also provided insufficient data. Because of the methodological inadequacies discussed earlier, the human data are considered inadequate to assess the carcinogenicity of benzoyl chloride. It should be noted, however, that benzotrichloride, which was one of the chemicals that

all the cancer patients were also exposed to (Sakabe et al., 1976), has been shown to cause tumors in mice exposed dermally or by inhalation (Yoshimura et al., 1979; Takemato et al., 1978).

5.2. MUTAGENICITY

With one questionable exception, benzoyl chloride was not found to be mutagenic in microbial assay systems. Negative results were obtained in reverse mutation assays in Salmonella typhimurium (±S-9, strains TA98, TA100, TA1535, TA1537, G46, C3076, D3052) (McMahon et al., 1979; Yasuo et al., 1978), in Escherechia coli (±S-9, strains WP2, WP2uvra$^-$ and Hs30R) (McMahon et al., 1979; Yasuo et al., 1978; Kawazoe and Kato, 1982) and in a rec assay with Bacillus subtilis (Yasuo et al., 1978). Chiu et al. (1978) reported negative results in the reverse mutation assay using S. typhimurium TA98, testing a dose range of 0.1-10 µmoles. In strain TA100, only a dose of 10 µmoles met the criteria for a positive result, i.e., induction of twice the number of revertants than the control. Yasuo et al. (1978) suggested that failure to observe benzoyl chloride-induced mutagenic activity might be related to the fact that benzoyl chloride readily hydrolyzes under experimental conditions. A detailed summary of these results is presented in Table 5-5.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of benzoyl chloride were not located in the available literature as cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects associated with exposure to benzoyl chloride were not located in the available literature as cited in the Appendix.

TABLE 5-5

Mutagenicity Testing of Benzoyl Chloride

Assay	Indicator/Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium strains TA1535, TA100, TA1537, TA98, G46, C3076, D3052	unspecified purity	plate incorporation	0.1-1000 µg/mL	±S-9	-	No data shown	McMahon et al., 1979
Reverse mutation	S. typhimurium strains TA1535, TA1536, TA1537, TA1538, TA98, TA100	unspecified purity	plate incorporation	NR	±S-9	-	No data shown*	Yasuo et al., 1978
Reverse mutation	S. typhimurium strains TA98, TA100	unspecified purity	plate incorporation	0.1-10 µmol/plate	none	+ for TA100 - for TA98	Response for TA100 is 2 times background at 10 µmoles only	Chiu et al., 1978
Reverse mutation	Escherichia coli strains, WP2 and WP2uvra	unspecified purity	plate incorporation	0.1-1000 µg/mL	±S-9	-	No data shown	McMahon et al., 1979
Reverse mutation	E. coli WP2 hcr	unspecified purity	plate incorporation	0, 2.1 or 3.6 µmol/plate	±S-9	-	None	Yasuo et al., 1978
Reverse mutation	E. coli Hs30R	unspecified purity	plate incorporation	NR	none	NR	No data shown	Kawazoe and Kato, 1982
Rec assay	Bacillus subtilis M45 (Rec⁻) H17 (Rec⁺)	unspecified purity	spot test	0.4 or 0.7 µmol/disk	none	NR	None	Yasuo et al., 1978

*Negative results may be due to the high susceptibility of benzoyl chloride to hydrolysis.

NR = Not reported

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5.5. CHRONIC AND SUBCHRONIC TOXICITY

Pertinent data regarding the chronic and subchronic toxicity of benzoyl chloride are limited. In a pulmonary carcinogenicity study on female ICR mice (see Section 5.1.), Takemoto et al. (1978) reported that mild adenoid proliferation was observed in 2/10 mice at the end of 10 months. Mice (n=20) were exposed by inhalation to 6.8 ppm (39.1 mg/m^3) benzoyl chloride for 30 minutes, 2 times/week for 5 months. Since other details were not reported, including whether control mice were used, the biological and statistical significance of this finding remains obscure.

In another pulmonary carcinogenicity study on female ICR mice (see Section 5.1.), Yoshimura et al. (1979) exposed an unspecified number of mice to an inferred concentration of 1.6 ppm (9.2 mg/m^3) of benzoyl chloride 2 times/week (30 minutes/exposure) for 5 months followed by observation periods of 1-10 additional months. Epithelial proliferation of the trachea was observed in 2/10 exposed mice at 10 months, but in none of the exposed mice examined at 6 or 14 months. Since other details, including control data, were not reported, the significance of this finding is also obscure.

In dermal carcinogenicity bioassays on ICR mice (see Section 5.1.), Fukuda et al. (1981) reported that benzoyl chloride exposure caused a decrease in motor activity as measured by a "motor activity monitor." Actual data were not presented. U.S. EPA (1982a) has interpreted this observation as an indication of neurotoxicity. Since benzoyl chloride is a dermal irritant (signs of irritation in mice included erythema, swelling, keratinization, alopecia, ulcers and epidermal necrosis), the restricted activity might have been due to pain associated with movement rather than to neurological effects per se. No other signs of toxicity were reported.

5.6. OTHER RELEVANT INFORMATION

U.S. EPA (1982a) reported the following:

> Benzoyl chloride is considered a strong irritant of the skin, eyes, nose and mucous membranes (ITII, 1975); short contact with the skin can result in second and third degree burns and vapors may cause eye and lung injury (Weiss, 1980).

Acute toxicity data for benzoyl chloride are summarized in Table 5-6.

5.7. SUMMARY

Evidence is insufficient to conclude that benzoyl chloride is carcinogenic (by inhalation or dermal routes of exposure) in mice (Fukuda et al., 1981; Yoshimura et al., 1979; Takemoto et al., 1978) or humans (Sakabe et al., 1976; Sakabe and Fukuda, 1977). There is, however, limited evidence that exposure to benzoyl chloride production or production of other chlorinated toluenes may be associated with an increased risk of respiratory cancer (Sakabe et al., 1976; Sorahan et al., 1983; Rockette and Arena, 1983; Wong and Morgan, 1984). Benzotrichloride is thought to be an etiologic agent in human respiratory cancer associated with benzoyl chloride production (IARC, 1982) since workers employed in benzoyl chloride or benzoyl peroxide production were also exposed to benzotrichloride which has been shown to cause cancer in mice by pulmonary and dermal routes of exposure (Yoshimura et al., 1979; Takemoto et al., 1978; Fukuda et al., 1981). Benzoyl chloride was not found to be mutagenic in bacterial assay systems (McMahon et al., 1979; Yasuo et al., 1978; Chiu et al., 1978; Kawazoe and Kato, 1982).

Pertinent data regarding the teratogenicity, reproductive toxicity and chronic or subchronic toxicity of ingested benzoyl chloride could not be located in the available literature as cited in the Appendix. Subchronic inhalation exposure of mice to 1.6 or 6.8 ppm (9.2 or 39.1 mg/m^3), 30

TABLE 5-6

Acute Toxicity of Benzoyl Chloride

Route	Species	Sex	LD_{50} or LC_{50}	Reference
Oral	rat	M	3619 mg/kg	Calo, 1977; Wazeter et al., 1974
	rat	F	1900 mg/kg	Calo, 1977; Wazeter et al., 1974
	rat	M/F	2618 mg/kg	Calo, 1977; Wazeter et al., 1974
		NR	2460 mg/kg	ITII, 1975
Inhalation	rat	NR	>2 to <200 mg/ℓ	Calo, 1977
Dermal	rat	NR	>2000 mg/kg	Calo, 1977
	rabbit	NR	790 mg/kg	ITII, 1975

NR = Not reported

minutes/day, 2 days/week for 5 months may have resulted in hyperplasia of the tracheal epithelium or adenoids (Takemoto et al., 1978; Yoshimura et al., 1979); however, the lack of control data compromises the reliability of these observations. In skin-painting studies designed to test the oncogenicity of benzoyl chloride, Fukuda et al. (1981) observed decreased motor activity in treated mice; however, the reduction in motor activity may have been due to pain associated with movement (benzoyl chloride caused skin irritation including erythema, swelling, keratinization, alopecia, ulcers and epidermal necrosis), rather than to neurological effects per se. Benzoyl chloride is considered to be strongly irritating to the skin, eyes, nose and mucous membranes (ITII, 1975; Weiss, 1980).

6. AQUATIC TOXICITY

6.1. ACUTE

Curtis et al. (1979) determined 24-, 48- and 96-hour LC_{50} values of 42.6, 34.7 and 34.7 mg/ℓ benzoyl chloride, respectively, for fathead minnows (Pimephales promelas). The 96-hour LC_{50} for grass shrimp (Palaemonetes pugio) was 180 mg/ℓ (Curtis et al., 1979). In water, benzoyl chloride rapidly hydrolyzes to hydrochloric acid and benzoic acid. The toxicity of benzoyl chloride, however, may have been caused by oxygen demand since, in the Curtis et al. (1979) grass shrimp study, the measured dissolved oxygen concentration was low enough (<1 mg/ℓ) to be toxic. Furthermore, most of the benzoyl chloride had decomposed. Based on measured rather than nominal concentrations, the 96-hour LC_{50} was 0.12 mg/ℓ rather than 180 mg/ℓ. Depending on the buffering capacity of the water, the pH depression caused by benzoic and hydrochloric acid may also have toxic effects on aquatic organisms.

6.2. CHRONIC

Pertinent data concerning chronic toxicity of benzoyl chloride could not be located in the available literature as cited in the Appendix.

6.3. PLANTS

Pertinent data concerning effects of benzoyl chloride on aquatic plants could not be located in the available literature as cited in the Appendix.

6.4. RESIDUES

Pertinent data concerning accumulation of benzoyl chloride in aquatic organisms could not be located in the available literature as cited in the Appendix. However, the rapid hydrolysis of benzoyl chloride in water makes uptake by aquatic organisms unlikely.

6.5. SUMMARY

The rapid hydrolysis and degradation of benzoyl chloride in water makes it difficult to assess its toxicity to aquatic organisms. Toxic effects are probably due to hydrolysis products, benzoic acid and hydrochloric acid, rather than benzoyl chloride itself (Curtis et al., 1979; U.S. EPA, 1982a).

7. GUIDELINES AND STANDARDS

7.1. HUMAN

U.S. EPA (1982a) reports the following guidelines and standards for benzoyl chloride:

1. A Romanian TLV of 5 mg/m³ with a MATC of 10 mg/m³ (U.S. EPA, 1982b; International Labour Office, 1980).
2. A MATC of 5 mg/m³ in the U.S.S.R. (U.S. EPA, 1982b; International Labour Office, 1980).
3. Discharges of ≥454 kg of benzoyl chloride into waterways must be reported to the U.S. EPA (U.S. EPA, 1982b; U.S. EPA, 1979).

Sources listed in the Appendix do not provide U.S. criteria or standards for ingestion or inhalation of benzoyl chloride.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of benzoyl chloride were not located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

There are insufficient data from which to derive quantitative criteria for either ingestion or inhalation of benzoyl chloride. There is insufficient evidence to conclude that benzoyl chloride is carcinogenic in mice by either pulmonary (Yoshimura et al., 1979; Takemoto et al., 1978) or dermal (Fukuda et al., 1981) routes of exposure. Benzoyl chloride alone has not been shown to be carcinogenic in humans, although benzoyl chloride production or production of chlorinated toluenes has been associated with an increased incidence of lung cancer (Sakabe et al., 1976; Sakabe and Fukuda, 1977; Sorahan et al., 1983; Rockette and Arena, 1983; Wong and Morgan, 1984). Problems with the above studies include small sample size and exposure to other chemicals especially benzotrichloride. Benzotrichloride administered by pulmonary or dermal routes of exposure has been shown to cause cancer in mice (Fukuda et al., 1981; Yoshimura et al., 1979; Takemoto et al., 1978). Benzoyl chloride was not shown to be mutagenic in bacterial assays (McMahon et al., 1979; Yasuo et al., 1978; Chiu et al., 1978; Kawazoe and Kato, 1982).

Pertinent data regarding the teratogenicity, reproductive toxicity or chronic toxicity of benzoyl chloride (any route of exposure) could not be located in the available literature as cited in the Appendix. In an inhalation carcinogenicity study, Takemoto et al. (1978) reported that mild adenoid proliferation was observed in 2/10 mice at the end of 10 months; exposure was 6.8 ppm (39.1 mg/m^3) benzoyl chloride, 2 times/week, 30 minutes/exposure for 5 months. Since other details were not reported, including whether or not controls were used, the significance of this finding remains obscure. In a similar study, Yoshimura et al. (1979) reported

that epithelial proliferation was observed in the tracheas of 2/10 mice at 10 months but not at 6 months. The mice were exposed to an inferred concentration of 1.6 ppm (9.2 mg/m^3) of benzoyl chloride 2 times/week, 30 minutes/exposure for 5 months. Control data were not presented. Again, the biological and statistical significance of this observation remains obscure. Fukuda et al. (1981) reported decreased motor activity in mice exposed dermally to benzoyl chloride (see Section 5.1.) for up to 11.7 months. U.S. EPA (1982a) has regarded this observation as an indication of neurotoxicity; however, the reduction in motor activity may have been due to pain associated with movement (benzoyl chloride caused skin irritation including erythema, swelling, keratinization, alopecia, ulcers and epidermal necrosis) rather than to neurotoxic effects per se.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY RANKING BASED ON CHRONIC TOXICITY

Pertinent data regarding the chronic toxicity of ingested or inhaled benzoyl chloride were not found in the available literature as cited in the Appendix.

In an inhalation carcinogenicity study on female ICR mice (see Section 5.1.), Takemoto et al., (1978) reported that mild adenoid proliferation was observed in 2 of 10 mice at the end of 10 months. Mice (n=20) were exposed by inhalation to 6.8 ppm (39.1 mg/m³) benzoyl chloride 2 times/week, 30 minutes/exposure for 5 months. Since other details were not reported, including whether or not controls were used, the biological and statistical significance of this finding remains obscure.

In another inhalation carcinogenicity study on female ICR mice (see Section 5.1.), Yoshimura et al. (1979) exposed an unspecified number of mice to an inferred concentration of 1.6 ppm (9.2 mg/m³) benzoyl chloride 2 times/week, 30 minutes/exposure for 5 months and observed for an additional 1-9 months. Epithelial proliferation of the trachea was observed in 2/10 exposed animals at 10 months but not at 6 or 14 months. Since other details, including control data, were not reported, the significance of this finding is also obscure.

These studies are not sufficient for use in the derivation of RQs (Table 9-1).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Carcinogenicity studies on benzoyl chloride have been discussed in detail in Section 5.1. Two inhalation studies on ICR mice, conducted as part of a larger study designed to investigate the carcinogenicity of benzotrichloride, yielded negative results (Yoshimura et al., 1979; Takemoto et

TABLE 9-1

Benzoyl Chloride

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	
Dose:	
Effect:	
Reference:	
RV_d:	
RV_e:	
Composite Score:	
RQ:	Data are not sufficient for deriving an RQ.

al., 1978). The study by Yoshimura et al. (1979) failed to report control data and the exposure concentration of benzoyl chloride, although an exposure concentration of 1.6 ppm (9.2 mg/m³) was implied. The study by Takemoto et al. (1978) was also vague about control data. Skin-painting studies on ICR mice yielded negative results (Fukuda et al., 1981), but only grossly defined tumors, and tissues of the lung were examined histologically. No potency factor can be derived from these data. IARC (1982) concluded that the skin-painting data are insufficient to support the hypothesis that benzoyl chloride is carcinogenic to animals. Likewise, the inhalation studies provided insufficient data.

Although there is insufficient evidence to support the carcinogenicity of benzoyl chloride in humans, there is limited evidence of an association between occupational exposure to benzoyl chloride and increased risk of lung cancer. This conclusion is derived primarily from an occupational exposure/epidemiology studies by Sakabe et al. (1976), Sorahan et al. (1983), Rockette and Arena (1983) and Wong and Morgan (1984) and case reports made by Sakabe and Fukuda (1977). These studies have been discussed in detail in Section 5.1. Weaknesses in the human studies include small sample size, exposure to other chemicals including benzotrichloride, lack of quantitative exposure data and the fact that the individuals who developed lung cancer were also smokers. Furthermore, benzotrichloride has been shown to cause tumors in mice exposed dermally or by inhalation (Fukuda et al., 1981; Yoshimura et al., 1979; Takemoto et al., 1978).

On the basis of the combined animal and human data, the U.S. EPA has determined that based on its proposed Cancer Risk Assessment Guidelines (U.S. EPA, 1984), benzoyl chloride is best classified as a Group D compound. This classification means there is no adequate animal or human evidence for carcinogenicity.

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN Internation
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in August, 1985 with the exception of the TOXLINE, which was searched in February, 1984 and was kindly supplied by Dynamac Corp. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1985-1986. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. p. 2878.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.

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Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

IARC (International Agency for Research on Cancer). 1982. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1984. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, N.I. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1984. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1985. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1985. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422. Washington, DC.

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Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.